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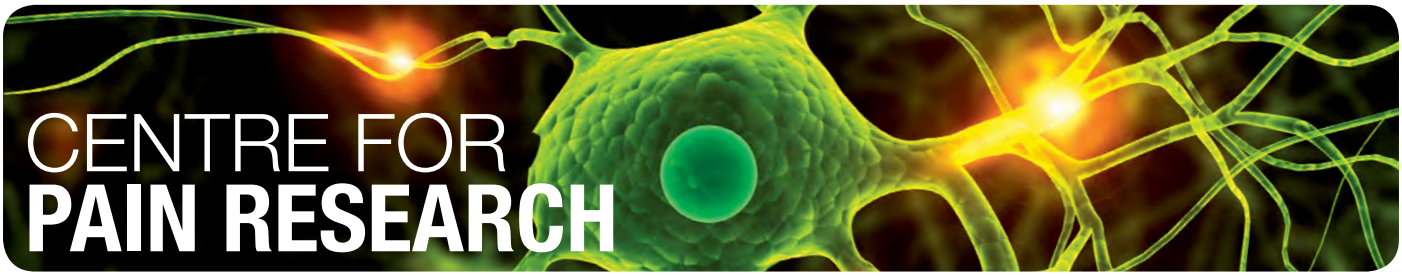
For scientists



CENTRE FOR PAIN RESEARCH

The vision of IMB's Centre for Pain Research (CPR) is to discover and develop new molecules for treating pain in humans. Specifically, we focus on pain that is difficult to manage, such as neuropathic, diabetic, chemotherapy and cancer pain. CPR researchers use advanced technologies to accelerate discovery and optimisation of analgesic small molecules, peptides, and natural products. We also examine their characterisation in disease and pathway-specific models of analgesic efficacy.

WHAT IS PAIN?

Pain is an unpleasant warning sign of tissue damage. It is usually transient in nature but can progress to chronic states that are challenging to treat.

One in five Australians, and one in three Australians over the age of 65, suffer from chronic pain, which remains one of the most under-recognised and under-treated medical problems.

The economic cost of treating chronic pain in Australia exceeds $34 billion per year, which is more than the cost of treating cancer, stroke, and diabetes. Many types of chronic pain (e.g. neuropathic pain) are poorly treated by current-generation analgesics ('painkillers') due to lack of efficacy and/or dose-limiting side effects. New classes of analgesics are required to better manage acute and chronic pain.

Our aim is to understand the mechanisms underlying the origins and transmission of pain, and to use this knowledge to produce more effective analgesics and improve quality of life for all Australians living with pain.

OBJECTIVES

- Develop a diverse repertoire of pharmacologically-characterised new molecules active in different pain pathways
- Improve our understanding of the molecular mechanisms underlying modality- and disease-specific pain pathways
- Isolate and characterise new research tools to delineate pain mechanisms and identify novel pain targets
- Develop and characterise new models of analgesic efficacy
- Identify new translational opportunities with industry partners
- Provide outstanding training and leadership in multidisciplinary pain research.

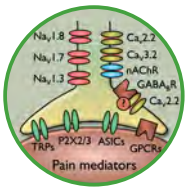
IMB PAIN RESEARCH

Discovery of novel analgesics

CPR uses a broad and comprehensive panel of assays for pain targets, addressing aspects of pain initiation and transmission using state-of-the-art screening technologies. Using unique compounds and libraries derived from natural products and venoms, these technologies place our research at the cutting edge of analgesic drug discovery.

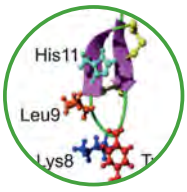
Structure-function

CPR uses advanced NMR and X-ray crystallographic approaches to obtain accurate three-dimensional structure of molecules and precisely position the residues contributing to affinity. This knowledge will be used to rationally optimise for target specificity, and, in parallel, will engineer out off-target liabilities to improve the therapeutic window of drug leads.



Analgesic efficacy models

CPR directly assesses analgesic efficacy of novel compounds in the pain pathway and clinically relevant disease models of pain. These approaches provide information to enable translation of our discoveries to the clinic by identifying preferred candidate molecules through to suitable patient populations, dosing routes, and strategies to minimise side effects in people living with pain.



Lead optimisation and development

Molecules showing significant analgesic efficacy in disease models of pain will be chemically modified to maximise storage and enzyme stability, ease of synthesis, and plasma half-life *in vivo*, without compromising therapeutic index, efficacy or safety.

INVESTIGATORS

- Richard Lewis (CPR Director)
- Paul Alewood
- Rob Capon
- Matt Cooper
- David Craik
- David Fairlie
- Glenn King
- Mark Smythe
- Rohan Teasdale
- Irina Vetter

COLLABORATORS

(Non-funding)

- Maree Smith (IMB Adjunct)
- Peter Cabot (UQ School of Pharmacy)
- Joe Lynch (QBI)
- Johan Rosengren, Walter Thomas (UQ SBMS)

EXTERNAL COLLABORATORS

- David Adams (RMIT)
- Stuart Brierley (University of Adelaide)
- Nigel Bunnett, Bill Charman, Joseph Nicolazzo (Monash Institute of Pharmaceutical Sciences)
- Brian Chait (Rockerfeller University, US)
- MacDonald Christie (University of Sydney)
- Arthur Christopoulos (Monash University)
- Michael Cousins (Pain Australia)
- Julia Fleming, Paul Gray (Royal Brisbane and Women's Hospital)
- Janet Hardy, John Hooper (Mater Research)
- David Julius (University of California, San Francisco, US)
- Michael Nitabach (Yale University, US)
- Steven Petrou (The Florey Institute)
- Christian Vaughan (Royal North Shore Hospital)
- John Wood (University College London)
- Katharina Zimmermann (University of Erlangen-Nuremberg, Germany)

COLLABORATORS

(Funding)

- National Health and Medical Research Council
- Australian Research Council
- Boehringer Ingelheim
- Janssen
- Alchemia

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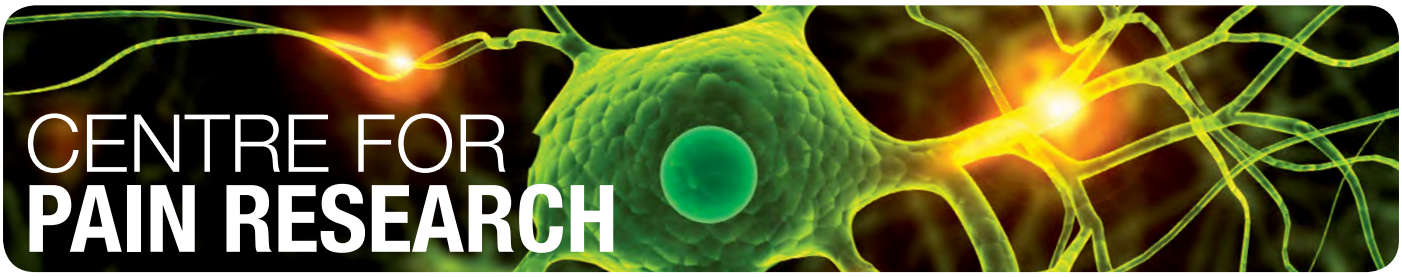

CENTRE FOR PAIN RESEARCH

PROFESSOR MAREE SMITH

Professor Maree Smith is an IMB adjunct and collaborator of the CPR. Professor Smith and her research team at the Centre for Integrated Preclinical Drug Development (CIPDD) focus on bringing innovation into new drug development methods. They assist drug discovery researchers in progressing their biomedical research intellectual property (IP) through various 'go/no-go' decision gates towards commercialisation. Professor Smith and her CIPDD team have a portfolio of 15 pain models that more closely mimic individual human pain conditions that are unique to Australia, but are rare internationally. Importantly, these are undertaken in a quality systems accredited laboratory environment at the CIPDD.
In addition, Professor Smith's patented IP of AT2R antagonists as novel analgesics for the relief of neuropathic and chronic inflammatory pain is in clinical development by the UQ spin-out company, Spinifex Pharmaceuticals.

RESEARCH APPROACHES

Professor Smith and her team have established and characterised a portfolio of sophisticated rodent pain models that more closely mimic individual human pain conditions. These models allow improved analgesic efficacy profiling of molecules from drug discovery programs in order to identify molecules that are more likely to be analgesic in humans. Professor Smith's discovery/translation research focus encompasses crucial research and development capabilities, including:

- analgesic efficacy profiling using a portfolio of sophisticated rodent pain models
- *ex vivo* mode of action investigations for potential novel analgesics using immunohistochemical and molecular biological methods
- bioanalytical method development; screening and fully validated as appropriate
- rodent pharmacokinetic studies
- metabolic stability assessment
- screening toxicology studies.

KEY PUBLICATIONS

Selected recent publications relevant to optimised and refined rodent pain models, analgesic efficacy profiling, and new drug development are as follows:

Khan N, Woodruff TM, **Smith MT** (2014) Establishment and characterization of an optimized mouse model of multiple sclerosis-induced neuropathic pain using behavioural, pharmacologic, histologic and immunohistochemical methods. *Pharmacol Biochem Behav* **126**:13-17.

Han YF, Wyse BD, **Smith MT** (2014) Optimisation and pharmacological characterization of a refined cisplatin-induced rat model of peripheral neuropathic pain. *Behav Pharmacol* (in press). Jul 15.

Muralidharan A, Wyse BD, **Smith MT** (2013) Optimization and characterization of a rat model of prostate cancer-induced bone pain using behavioural, pharmacological, radiological, histological and immunohistochemical methods. *Pharmacol Biochem Behav* **106**: 33-46.

Smith MT, Wyse BD, Edwards SR (2013) Small Molecule Angiotensin II Type 2 receptor (AT2R) Antagonists as Novel Analgesics for Neuropathic Pain: Comparative Pharmacokinetics, Radioligand Binding and Efficacy in Rats. *Pain Med* **106**: 33-46.

Smith MT, Woodruff Wyse BD et al. (2013) A small molecule angiotensin II type 2 receptor (AT2R) antagonist produces analgesia in a rat model of neuropathic pain by inhibition of p38 mitogen activated protein kinase (MAPK) and p44/p42 MAPK activation in the dorsal root ganglia. *Pain Med* **14**: 1557-68.